Remarks/Arguments

Claims 119-126 and 129-131 are pending in this application.

I. 35 U.S.C. §§ 101 and 112, First Paragraph –Utility/Enablement

Claims 119-126 and 129-131 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants strongly disagree and, therefore, respectfully traverse the rejection.

Applicants submit that the data presented in Example 170 starting on page 539 of the specification, and the cumulative evidence of record, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention. Applicants rely upon the gene amplification data of the PRO1153 gene for patentable utility of the claimed PRO1153 polypeptides. This data is clearly disclosed in the instant specification in Example 170, which discloses that the gene encoding PRO1153 showed significant amplification in primary lung tumors. As disclosed in previous response on record, Applicants submit that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly over expressed and has utility in the diagnosis of lung cancer or for individuals at risk for developing lung cancer.

As further support for their utility claim, Applicants have submitted a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. According to the Goddard Declaration, the 2.0-fold to 2.9-fold amplification of PRO1153 in adenocarcinomas or squamous cell carcinomas of the lung would be considered significant and credible by one skilled in the art, based upon the facts disclosed therein. The

Examiner has not provided any evidence to show that the disclosed DNA amplification is not significant.

The Examiner asserts that basis of the rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels. (Page 3 of the instant Office Action).

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (submitted with Response of June 25, 2004) collectively teach that in general, gene amplification increases mRNA expression.

Further, Applicants have submitted a Declaration of Dr. Paul Polakis, which teaches that, in general, there is a correlation between mRNA levels and polypeptide levels. Applicants would also like to bring to the Examiner's attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO1153 polypeptide to refute Appellant's assertion of a correlation between DNA levels, mRNA levels and protein expression.

Applicants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede to), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Applicants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna et al. (made of record in the Response submitted June 25, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as

exemplified by the teachings of Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, the art in general overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung cancers.

Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed antibodies to PRO1153 polypeptides.

The Examiner has further asserted that "[o]nly two out of the fourteen lung cancer samples tested positive. Therefore, if a sample were taken from an individual with actual lung cancer, ***it is more likely than not that this assay would yield a false negative result****" (Page 4 of the instant Office Action, emphasis in original).*

Applicants emphasize that they have shown significant DNA amplification in two of the lung tumor samples in Table 9, Example 170 of the instant specification. The fact that not all lung tumors tested positive in this study does not make the gene amplification data less significant. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. For example, the article by Hanna and Mornin (of record), discloses that the known breast cancer marker HER-2/neu is "amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma" (page 1, col. 1). In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are useful for better classification of tumors. Therefore, whether the PRO1153 gene is amplified in two lung tumors or in all lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO1153 is considered significant is what lends support to its usefulness as a tumor marker.

The Examiner has also asserted that "[t]he data presented in the specification were not corrected for aneuploidy" and cites a references by Hittelman et al. and Sen et al. in support of the assertion that "[a] slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." (Page 5 of the instant Office Action).

Applicants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Response filed June 25, 2004),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

The Examiner has asserted that "[s]ignificant further research is would have been required of the skilled artisan to reasonable confirm that PRO1153 is overexpressed in any cancer to the extent that I could be used as a cancer diagnostic agent, thus the asserted utility is not substantial." (Page 7 of the instant Office Action).

As discussed in previous responses of record, M.P.E.P. §2107.01 cautions Office personnel not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an Appellant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[1] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[2] gives the following instruction to patent examiners: "If the

[1] M.P.E.P. §2107.01.

Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Applicants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO274 is significantly amplified in certain lung tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO1153 gene is amplified, the PRO1153 polypeptide would be more likely than not over-expressed. Thus, data relating to PRO1153 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO1153 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed PRO1153 polypeptides, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Applicants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to PRO1153 polypeptide expression and that the claimed PRO1153 polypeptides have utility in the diagnosis of cancer.

A *prima facie* case of lack of utility has not been established

Applicants respectfully submit that the Examiner has not made a proper *prima facie* showing of lack of utility, because the Examiner has not shown that Applicants' asserted utility is more likely than not incorrect.

The Examiner asserts that "[t]he art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels", citing Pennica, Konopka, Sen, Godbout and Li (pages 4-7 of the instant Office Action).

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA

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[2] M.P.E.P. §2107 II(B)(1).

and polypeptide levels. As discussed in the previous responses of record, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants have previously cited Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* as collectively teaching that in general, gene amplification increases mRNA expression. Applicants' arguments presented in the previously filed Response submitted June 25, 2004 and Preliminary Amendment submitted July 24, 2007are hereby incorporated by reference in their entirety.

Pennica *et al.*

The Examiner has cited the abstract of Pennica *et al.* for its disclosure that "WISP-2 genomic DNA was amplified in colon cancer cell lines and in human colon tumors, but RNA expression was reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (Page 5 of the instant Office Action). From this, the Examiner has concluded that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist.

Nowhere in the Pennica paper does the author suggest that it is more likely than not that altered mRNA levels does not correlate with altered protein levels. On the contrary, there is a statement in Pennica that says "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression...*" (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added), which implies

that the mRNA/protein correlation does exist, even if not always, but "always" is not required by the utility standard.

The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression . . . .*" (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added). Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Konopka *et al.*

The Examiner has also citeded the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to gene amplification but to variation in the level of mRNA produced from a single genomic template." (Page 5 of the instant Office Action).

Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka *et al.* does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone. Nor does Konopka *et al.* support the PTO's position that DNA amplification is not correlated with mRNA overexpression. Konopka *et al.* show only that, of the cell lines known to have increased abl protein expression, only one had amplification of the abl gene (page 4051, col. 1). This result proves only that increased mRNA and protein expression levels can result from causes other than gene amplification. Konopka *et al.* do not demonstrate that when gene amplification does occur, it does not result in increased mRNA and protein expression levels, particularly given that the cell line with amplification of the abl gene did show increased abl mRNA and protein expression

levels. Applicants further submit that, contrary to the PTO's assertions, Konopka *et al.* supports Applicants' position that mRNA levels correlate with protein levels. Konopka *et al.* states that "the 8-kb mRNA that encodes $P210^{c\text{-}abl}$ was detected at a 10-fold higher level in SK-CML7bt-333 (Fig. 3A, +) than in SK-CML16Bt-1 (B, +), which **correlated** with the relative level of $P210^{c\text{-}abl}$ detected in each cell line. Analysis of additional cell lines demonstrated that the level of 8-kb mRNA **directly correlated** with the level of $P210^{c\text{-}abl}$ (Table 1)" (page 4050, col. 2, emphasis added).

Thus, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to single genes or genes within a single family and thus, their teachings have been misinterpreted in this rejection.

Godbout *et al.*

Regarding Godbout, the Examiner has asserted that Godbout et al. teaches that "a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The Examiner further asserts that Godbout teaches "[i]t is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell." (Page 6 of the instant Office Action).

Applicants have previously made of record three more recent references, published in 2002, by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al*, (made of record in Applicants' Response filed on June 25, 2004), which collectively teach that in general, gene amplification increases mRNA expression. Applicants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout *et al.* Nevertheless, Applicants maintain that Godbout *et al.* report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer. Mechanistic data is not a requirement for the utility requirement. Hence, this rejection is improper. Applicants respectfully submit that, as discussed above, Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (of record), collectively teach that gene amplification increases mRNA expression for large numbers of genes, which have not been identified as being

oncogenes or as conferring any selective growth advantage on tumor cells. Thus, the art of record clearly shows that there is no requirement that a polypeptide must be a known oncogene or a protein otherwise known to be associated with tumor growth, in order for amplification of the gene encoding the protein to correlate with increased protein expression. In fact, as demonstrated by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, examination of gene amplification is a useful way to identify novel proteins not previously known to be associated with cancer.

Li *et al.*

The Examiner also cites Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 7 of the instant Office Action). Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants' previous responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above, the PRO1153 gene showed 2.0 fold to 2.9-fold amplification in adenocarcinomas or squamous cell carcinomas of the lung, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO1153, would be expected to show a corresponding increase in transcript expression.

The Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants

that PRO1153 has utility. As discussed above, the law does not require that DNA amplification is "always" associated with overexpression of the gene product. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

II. 35 U.S.C. §112, First Paragraph –Written Description

Claims 119-123 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. (Page 8 of the instant Office Action).

In particular, the Examiner has asserted that "Applicants were not in possession of all or a significant number of polypeptides that have 80-99% homology to SEQ ID NO: 351, while retaining the function of SEQ ID NO: 351." The Examiner adds that allegedly, Appllicants have not described a representative number of species that have 80-99% homology to SEQ ID NO: 351, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 351 (Page 9 of the instant Office Action).

Applicants respectfully maintain the position that Claims 119-123 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in Applicants' Response submitted June 25, 2004 and Preliminary Amendment submitted July 24, 2007.

Applicants therefore respectfully request the Examiner to reconsider and withdraw the written description rejection of Claims 119-123 under 35 U.S.C. §112, first paragraph.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **07-1700** (Attorney Docket No.: **39780-2730P1C31**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: March 17, 2008

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte AUDREY GODDARD, PAUL J. GODOWSKI,
AUSTIN L. GURNEY, VICTORIA SMITH, and WILLIAM I. WOOD

Appeal 2006-1469
Application 10/123,212
Technology Center 1600

Decided: April 30, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 72-79 and 82-84. We have jurisdiction under 35 U.S.C. § 6(b). Claims 72 and 77 are representative of the claims on appeal, and read as follows:

72. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:14;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:14, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577,

wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells.

77. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:14;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:14, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577.

Claims 72-79 and 82-84 stand rejected under 35 U.S.C. § 101 as not being supported by either a specific and substantial utility or a well-established utility. Claims 72-76, 83, and 84 stand rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification, and claims 72-76, 83, and 84 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. Finally, 72-74, 83, and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Young,[1] and claims 72-75, 83, and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Stanton.[2]

We Affirm-In-Part.

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[1] Young, US Patent No. 6,525,174 B1, issued February 25, 2003.
[2] Stanton, US Pub. No. 2002/0110804 A1, published August 15, 2002.

UTILITY

ISSUE

The Examiner contends that the Specification fails to establish a specific and substantial utility or a well-established utility of the polypeptide of SEQ ID NO:14.

Appellants contend that Example 30 presents microarray data demonstrating that the polypeptide of SEQ ID NO:14 is a diagnostic marker for colon, lung, and prostate tumors.

The issue is thus whether the microarray data presented in Example 30 of the Specification is sufficient to establish a specific and substantial utility or a well-established utility for the polypeptide of SEQ ID NO:14?

FACTS

The Examiner rejected claims 72-79 and 82-84 under 35 U.S.C. § 101 as not being supported by either a specific and substantial asserted utility or a well-established utility (Answer 4).

The Examiner notes that the Specification discloses the polypeptide of SEQ ID NO:14 (PRO1866), the nucleic acid sequence encoding it (SEQ ID NO:13), as well as antibodies against the polypeptide. (*Id.*)

As to a well-established utility, the Examiner asserts that the prior art does not demonstrate that the polypeptide of SEQ ID NO:14, the nucleic acid encoding the polypeptide or an antibody that binds to the polypeptide, has "any well-established biological functions or any physiological significance." (*Id.* at 4-5.)

Next, as to a specific and substantial utility, the Examiner references Table 8 of the Specification, which states that the polypeptide is

significantly overexpressed in colon, lung, or prostate tumors compared to a non-cancerous human tissue control. (*Id.* at 5.) The Examiner also notes that the statement is based on a microarray analysis, which measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. (*Id.*) According to the Examiner:

> There is no sufficient information or experimental data presented on whether the polypeptide or the nucleic acid of the present invention can serve as a reliable diagnostic marker for colon, lung or prostate tumors; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of colon, lung or prostate tumors without undue experimentation. Accordingly, the results in Table 8 obtained based upon the assay described in Example 30 only serve as the beginning point for further research on the biological functions or physiological significance of the polypeptide of SEQ ID NO:[]14 or the nucleic acid encoding the polypeptide, and does not provide a specific and substantial utility for the present invention.

(*Id.* at 5-6.)

Appellants argue that patentable utility is demonstrated by Example 30 of the Specification (Br. 4). According to Appellants, Example 30 demonstrates that the gene encoding the polypeptide of PRO1866 (SEQ ID NO:14) "showed significant overexpression in colon, lung, and prostate tumors as compared to a universal normal control," demonstrating "'that the PRO polypeptides of the present invention are useful . . . as diagnostic markers for the presence of one or more cancerous tumors . . . .'" (*Id.*)

Appellants argue further that it is legally incorrect for the Examiner to require specific data, statistical analysis, and further details before accepting the utility set forth in the Specification, as the law is clear that the Examiner must accept Appellants' assertion of utility if that assertion would be credible to one of ordinary skill. (*Id.* at 4-5.)

Appellants assert that the Examiner has used an improper standard in asserting that mRNA levels do not necessarily correlate with the protein level and that protein levels cannot be accurately predicted from mRNA levels. (*Id.* at 6.) The evidentiary standard to be used during examination is preponderance of the evidence under the totality of the circumstances, and thus, Appellants argue, the Examiner "must establish that it is *more likely than not* that one of ordinary skill in the art would doubt the truth of the statement of utility," which "is a much lower standard than a 'necessary' correlation or 'accurate' prediction, and is clearly met for the invention claim." (*Id.* (emphasis in original)).

Moreover, Appellants rely on the Declaration of Dr. Paul Polakis, which states that "*in general, there is a correlation between mRNA levels and polypeptide levels.*" (Br. 6 (emphasis in original)). Appellants also rely on the Declaration of Dr. Victoria Smith, which states that "*microarray analyses actually performed in my laboratory* have shown that when molecules are identified as being overexpressed in a human tumor sample of epithelial origin relative to the 'universal normal control'[3] sample, *in a majority of cases*, that molecule is also confirmed as being overexpressed in

[3] The "universal" epithelial control sample is prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung (Br. 12).

the human tumor tissue sample relative to its human tissue counterpart" (Br. 6 (emphasis in original)). Appellants aver that the two declarations support the assertion of utility in the Specification, *i.e.*, that the PRO1866 polypeptide (SEQ ID NO:14) "is reasonably expected to be overexpressed in colon, lung and prostate tumors and can be used as a cancer diagnostic marker." (*Id.* at 6-7.)

The Specification is drawn to the identification and isolation of novel DNA and to the recombinant production of polypeptides (Specification 1).

Example 30 on page 134 of the Specification is drawn to microarray analysis to detect PRO polypeptides in cancerous tumors.

According to the Specification:

> In the present example, cancerous tumors derived from various human tissues were studied for PRO polypeptide-encoding gene expression relative to non-cancerous human tissue in an attempt to identify those PRO polypeptides which are overexpressed in cancerous tumors. Two sets of experimental data were generated. In one set, cancerous human colon tumor tissue and matched non-cancerous human colon tumor tissue from the same patient ("matched colon control") were obtained and analyzed for PRO polypeptide expression using . . . microarray technology. In the second set of data, cancerous human tumor tissue from any of a variety of different human tumors was obtained and compared to a "universal" epithelial control sample which was prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung. mRNA isolated from the pooled tissues represents a mixture of expressed gene products from these different tissues. Microarray hybridization experiments using the pooled control samples generated a linear plot in a 2-color analysis. The slope of the line generated in a 2-color analysis was then used to normalize the ratios of (test:control detection) within each experiment. The normalized ratios from various experiments were then compared and used to identify clustering

> of gene expression. Thus, the pooled "universal control" sample not only allowed effective relative gene expression determinations in a simple 2-sample comparison, it also allowed multi-sample comparisons across several experiments.
>
> In the present experiments, nucleic acid probes derived from the herein described PRO polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from the tumor tissues listed above were used for the hybridization thereto. A value based upon the normalized ratio:experimental ratio was designated as a "cutoff ratio". Only values that were above this cutoff ratio were determined to be significant. Table 8 below shows the results of these experiments, demonstrating that various PRO polypeptides of the present invention are significantly overexpressed in various human tumor tissues as compared to a non-cancerous human tissue control. As described above, these data demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

(*Id.* at 134-35.)

As to PRO1866, the Specification presents Table 8, which states that PRO1866 is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. (*Id.* at 135.)

The Declaration of Dr. Paul Polakis, dated September 9, 2005, states in paragraphs 4 and 5 that, based on experience with other gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells, it has been observed "that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the

level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells."

The Declaration of Dr. Victoria Smith at paragraph 5, dated September 9, 2005, states that the comparison of mRNA expression levels in human tumor tissues to mRNA expression levels in a sample prepared by pooling non-cancerous human tissues of epithelial origin "is extremely informative and provides a strong basis for the diagnostic determination of cancer in humans."

PRINCIPLES OF LAW

The examiner bears the initial burden of showing that a claimed invention lacks patentable utility. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

The Court of Appeals for the Federal Circuit addressed the utility requirement in *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility." 421 F.3d at 1370, 76 USPQ2d at 1229. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at 1371, 76 USPQ2d at 1229. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to

satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." *Id.*, 76 USPQ2d at 1230.

The court held that a specific utility is "a use which is not so vague as to be meaningless." *Id.* In other words, "in addition to providing a 'substantial' utility, an asserted use must show that that the claimed invention can be used to provide a well-defined and particular benefit to the public." *Id.*

ANALYSIS

We find that the microarray data presented in Example 30 of the Specification is sufficient to establish a specific and substantial utility for the polypeptide of SEQ ID NO:14, and the rejection is reversed.

The microarray data demonstrates that mRNA for the PRO1866 polypeptide (SEQ ID NO:14) is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. Thus, the polypeptide of SEQ ID NO:14 has a significant and presently available benefit to the public as a tumor marker.

We have considered the Examiner's assertions that microarray analysis measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. As demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that.

Finally, the use of the PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility, and there is no requirement that a causative

link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors be demonstrated.

ENABLEMENT

ISSUE

The Examiner contends that the disclosure does not enable one skilled in the art to practice the full genus of peptides encompassed by Appellants' claims.

Appellants contend that one skilled in the art could practice the full scope of the claimed invention, as the skilled artisan has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:14, and the specification provides ample guidance such that one of skill in the art could readily test the nucleic acid encoding a variant polypeptide to determine whether it is overexpressed in colon, lung or prostate tumors by the methods set forth in Example 30.

Thus, the issue is does the Specification enable one skilled in the art to use the full scope of the PRO1866 (SEQ ID NO:14) variants of claim 72 without an undue amount of experimentation?

FACTS

The Examiner rejected claims 72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph, on the grounds that the instant disclosure does not enable the full scope of the claimed subject matter (Answer 7).[4]

As we find that Appellants do not argue the claims separately, we focus our attention on independent claim 72. 37 C.F.R. § 41.37(c)(1)(vii) (2006).

The Examiner made the following findings with respect to the factors set out in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).[5]

The breadth of the claims: The Examiner notes that the claims are broad and encompass a genus of variants of SEQ ID NO:14 (Answer 8).

Nature of the invention and the state of the prior art: The Examiner notes that while the Specification teaches that the polypeptide of SEQ ID NO:14 is overexpressed in colon, lung or prostate tumors, the polypeptide "does not have any defined biological functions or activities." (*Id.*)

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[4] The Examiner also rejected claims 72-79 and 82-84 under 35 U.S.C. § 112, first paragraph, on the grounds that "since the claimed invention is not supported by either a specific and substantial utility or a well established utility . . ., one skilled in the art clearly would not know how to use the claimed invention" (Answer 7). Since that rejection relies on the utility rejection, and as we have reversed that rejection, this rejection is also reversed.

[5] The factual considerations discussed in *Wands* are: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Examiner notes further that two variants of the polypeptide of SEQ ID NO: 14 are taught in the prior art by Young (a variant having 92.5% homology) and Stanton (a variant having 96.7% identity), but does not teach that the variants are overexpressed in colon, lung, or prostate tumor cells (Answer 8-9). The Examiner also asserts, citing Haynes,[6] that even if the amount of nucleic acid expressed from SEQ ID NO:13 was overexpressed in colon, lung, or prostate tumor cells, it does not necessarily follow that the polypeptide of SEQ ID NO:14 would also be overexpressed.

The amount of direction or guidance presented and the existence of working examples: The Examiner states that, other than for the polypeptide of SEQ ID NO:14, the Specification fails to provide sufficient direction and/or working examples to make those variants that have the same functions as SEQ ID NO:14, and that there are no examples of functional variants of SEQ ID NO:14 (Answer 9). The Examiner notes further that the Specification does not teach which residues are critical to activity, and thus which modifications will results in a variant having the same function as that of SEQ ID NO:14. (*Id.* at 9-10.)

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary: While acknowledging that the level of skill in the art of DNA recombination technology is relatively high, the Examiner states that procedures for making

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[6] Haynes et al. (Haynes), "Proteome analysis: Biological assay or data archive," *Electrophoresis*, Vol. 19, pp. 1862-1871 (1998). The Examiner cites Haynes for the proposition that "[t]he prior art teaches that the multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (Answer 9).

variants of the polypeptide of SEQ ID No: 14 as set forth by the claims that still retain its activity are not conventional and are unpredictable. (*Id.* at 10.) The Examiner concludes that "due to lack of the disclosure of the functions of encompassed polypeptides structurally related to SEQ ID NO:14, [lack of] sufficient guidance and/or working examples provided in the specification, and [lack of] teachings in the art on how to use those variants of the polypeptide of SEQ ID NO:14, it would take undue experimentation for one skilled in the art to make and use the variants of polypeptide of SEQ ID NO:14." (*Id.* at 10-11.)

Appellants argue that "the claimed variants all share the functional limitation that '*the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells*," and that Example 30 of the Specification provides step-by-step guidelines and protocols for the microarray analysis (Br. 28 (emphasis in original)). Appellants assert further that "[t]he specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 81, line 17, to page 83, line 26)" (Br. 29).

Appellants submit

> that the specification provides ample guidance such that one of skill in the art could readily test the nucleic acid encoding a variant polypeptide to determine whether it is overexpressed in colon, lung or prostate tumors by the methods set forth in Example 30. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:14. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.
>
> The claims currently recite polypeptide sequences associated with a specific biological activity of the encoding nucleic acid. This biological activity together with the well

> defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation.

(*Id.*)

As noted with respect to the utility rejection, Table 8 of the Specification states that PRO1886 is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. (Specification 135.)

Page 81, line 17 to page 83, line 26 of the Specification provides general guidance as to the generation of PRO polypeptide variants, which guidance is applicable to the generation of any polypeptide variant. The Specification does not disclose any guidance that is specific to the PRO1866 (SEQ ID NO:14) polypeptide. The Specification also does not present any data as to the biological function of PRO1866 other than the microarray data that demonstrates that it may be used as a tumor marker.

PRINCIPLES OF LAW

Enablement is a question of law, based on underlying findings of fact. *See, e.g., In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the

invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright*, 999 F.2d at 1561, 27 USPQ2d at 1513 (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138 (Fed. Cir. 1999).

"Patent protection is granted in return for an enabling disclosure . . . , not for vague intimations of general ideas that may or may not be workable." *Genentech*, 108 F.3d at 1365, 42 USPQ2d at 1005. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention." *Id.* at 1366, 42 USPQ2d at 1005 (emphasis added).

ANALYSIS

While Appellants have demonstrated that the polypeptide of SEQ ID NO:14 is a diagnostic marker for colon, lung, and prostate cancer, the Specification sets forth no biological activity or function for the protein. All

that is disclosed is the sequence information for SEQ ID NO:14. Moreover, the Specification does not disclose which portions of the polypeptide of SEQ ID NO:14 are required for activity, and which regions are tolerant to substitution. With respect to the variants, all that is disclosed by the Specification are methods of making polypeptide variants in general, and information as to what amino acid substitutions are generally considered by the skilled artisan to be conservative. The Specification, however, does not disclose any guidance of generating variants of the polypeptide of SEQ ID NO:14 that is specific to SEQ ID NO:14, wherein the variant is overexpressed in colon, lung, or prostate tumor cells.

Without information as to the biological activity or function, it would be unpredictable to the skilled artisan which variants of SEQ ID NO:14 would also perform as a diagnostic marker for colon, lung, and prostate cancer. Claim 72 is drawn to variants having 80% amino acid sequence identity, but, as noted by the Examiner, two variants of the polypeptide of SEQ ID NO:14 having higher sequence identity have been disclosed by Young (a variant having 92.5% homology) and by Stanton (a variant having 96.7% identity), but have not been shown to be overexpressed in colon, lung, or prostate tumor cells.

Given the lack of guidance as to the biological function or activity of the polypeptide of SEQ ID NO:14, and the lack of guidance as to those variants of SEQ ID NO:14 that would be expected to also perform as a diagnostic marker for colon, lung, and prostate cancer, as well as the enormous number of variants that would have 80% sequence identity with

SEQ ID NO:14,[7] it would require an undue amount of experimentation by one skilled in the art to use the full scope of variants encompassed by claim 72 without further guidance from Appellants.

CONCLUSIONS OF LAW

We conclude that the Specification does not enable one skilled in the art to use the full scope of the PRO1866 (SEQ ID NO:14) variants of claim 72 without an undue amount of experimentation, and the rejection is affirmed.

WRITTEN DESCRIPTION

ISSUE

The Examiner contends that the claims are drawn to an isolated polypeptide having 80%, 85%, 90%, 95%, and 99% sequence identity to SEQ ID NO:14, and due to the breadth of the claimed genus and the lack of definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Appellants were in possession of the claimed genus

Appellants contend that the genus of polypeptides with at least 80% sequence identity to SEQ ID NO:14, which possess the functional property of having a nucleic acid which is overexpressed in colon, lung or prostate tumors, would meet the requirement of 35 U.S.C. § 112, first paragraph, as providing adequate written description.

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[7] The polypeptide of SEQ ID NO:14 is 541 amino acids long, and as there are 20 naturally occurring peptides, the number of variants that would have 80% sequence identity to SEQ ID NO:14 would be enormous.

Thus, the issue is does the disclosure as filed provide adequate written description to support the genus of variants of the polypeptide of SEQ ID NO:14 encompassed by claim 72?

FACTS

The Examiner rejected claims 72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (Answer 11).

As we find that Appellants do not argue the claims separately, we focus our attention on independent claim 72. 37 C.F.R. § 41.37(c)(1)(vii) (2006).

The Examiner notes that the claims are drawn to an isolated polypeptide having 80%, 85%, 90%, 95%, and 99% sequence identity to SEQ ID NO:14, asserting that the claims do not require that the polypeptide have any particular conserved structure or any other distinguishing feature. (Answer 12.) According to the Examiner,

> [w]hile the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells," such a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells. Thus, the claims are drawn to a genus of polypeptides that is defined only by a partial structure in the form of a recitation of percent identity.

(*Id.*)

Moreover, according to the Examiner, the disclosure of SEQ ID NO:14 and its encoding nucleic acid sequence, SEQ ID NO:13, "does not adequately support the scope of the claimed genus, which encompasses a substantial variety of homologues or variants of the polypeptide of SEQ ID NO:14." (*Id.*) The disclosure as filed, the Examiner asserts, fails to provide sufficient description as to structural and functional features of the claimed genus, such as conserved regions that are critical to the structure and function of the genus claimed. (*Id.* at 13.) Thus, "[t]here is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function." (*Id.*)

The Examiner concludes:

> Due to the breadth of the claimed genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genus. Accordingly, only the isolated polypeptide comprising SEQ ID NO:14 . . ., but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph.

(*Id.* at 13-14.)

Appellants assert that "the genus of polypeptides with at least 80% sequence identity to SEQ ID NO:14, which possess the functional property of having a nucleic acid which is overexpressed in colon, lung or prostate tumors would meet the requirement of 35 U.S.C. § 112, first paragraph, as providing adequate written description." (Br. 32.) According to Appellants, the level of skill in the art of recombinant DNA technology is high, and thus "the teachings imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made." (*Id.*)

Appellants argue further that Example 30 provides step-by-step guidelines and protocols for performing the microarray analysis, thus the skilled artisan could test variants of the PRO1866 polypeptide (SEQ ID NO:14) to determine if they are overexpressed in colon, lung, or prostate tumor cells. (*Id.*) Moreover, Appellants aver, the Specification (page 81, line 17, to page 83, line 26) provides detailed guidance as to what changes may be made to the PRO polypeptide without affecting its activity, such as exemplary and preferred amino acid substitutions (Br. 33). "Accordingly," Appellants assert, "one of skill in the art could identify whether a variant PRO1866 sequence falls within the parameters of the claimed invention." (*Id.*).

Appellants note that factors to be considered in evidencing possession of a claimed genus include structural features and functional activity, which they assert they have provided by reciting a structural feature—80% sequence identity to SEQ ID NO:14—as well as a specific functional activity for the encoding nucleic acids. (*Id.*)

As noted above with respect to the enablement rejection, page 81, line 17 to page 83, line 26 of the Specification provides general guidance as to the generation of PRO polypeptide variants. The Specification does not disclose any guidance that is specific to the PRO1866 (SEQ ID NO:14) polypeptide. The Specification also does not present any data as to the biological function of PRO1866 other than the microarray data that demonstrates that it may be used as a tumor marker.

PRINCIPLES OF LAW

The requirement for written description under the first paragraph of section 112 is separate and distinct from the enablement requirement of that paragraph. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991). Compliance with the written description requirement is a question of fact. *Id.*

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997 (bracketed material in original). The claims in *Lilly* were directed generically to vertebrate or mammalian insulin cDNAs. *See id.* at 1567, 43 USPQ2d at 1405. The court held that a structural description of a rat cDNA was not an adequate description of these broader classes of cDNAs.

The *Lilly* court explained that

> a generic statement such as. . . 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

Id. at 1568, 43 USPQ2d at 1406. Finally, the *Lilly* court set out exemplary ways in which a genus of cDNAs could be described:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by

> nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Id. at 1569.

Our appellate reviewing court revisited the issue of describing DNA. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court held that a claimed DNA could be described without, necessarily, disclosing its structure. The court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" *See id.* at 1324, 63 USPQ2d at 1613 (emphasis omitted, ellipsis and bracketed material in original).

Our appellate review court has also noted that "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003).

This standard applies to polypeptides as well as DNAs. *See University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 925, 69 USPQ2d 1886, '893 (Fed. Cir. 2004): "We agree with Rochester that *Fiers*,

Lilly, and *Enzo* differ from this case in that they all related to genetic material whereas this case does not, but we find that distinction to be unhelpful to Rochester's position. It is irrelevant; the statute applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue."

With respect to the use of an assay to support written description, in *University of Rochester*, the patent claimed a method of selectively inhibiting the enzyme PGHS-2 (also known as COX-2) by "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human." *Id.* at 918, 69 USPQ2d at 1888. The patent "described in detail how to make cells that express either COX-1 or COX-2, but not both . . . , as well as 'assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product.[']" *Id.* at 927, 69 USPQ2d at 1895.

The court held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of *which* peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. *See id.* ("As pointed out by the district court, the '850 patent does not disclose just 'which "peptides, polynucleotides, and small organic molecules" have the desired characteristic of selectively inhibiting PGHS-2.' . . . Without such disclosure, the claimed methods cannot be said to have been described.").

ANALYSIS

We find that the disclosure as filed does not provide adequate written description to support the genus of variants of the polypeptide of SEQ ID NO:14 encompassed by claim 72, and the rejection is affirmed.

Claim 72 is drawn to variants that have 80% sequence identity to SEQ ID NO:14, wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells. The Specification does not disclose a biological function or activity of the polypeptide of SEQ ID NO:14, and also does not disclose a single variant that also performs as a diagnostic marker for colon, lung, and prostate cancer. Thus, the genus encompasses an enormous number of sequences, but the Specification only describes a single member of that genus—SEQ ID NO:14.

In addition, there is no disclosure of sufficiently detailed, relevant identifying characteristics, such as other physical and/or chemical properties, or functional characteristics, that when coupled with a known or disclosed correlation between function and structure (i.e., the sequence), or some combination of such characteristics, would constitute an adequate written description of the claimed invention. All that is disclosed is the amino acid sequence and that it may be used as a diagnostic marker for certain tumor types. While the skilled artisan may be able to determine polypeptides that have 80% sequence identity with SEQ ID NO:14, without any disclosure of function or what residues are required for the polypeptide to function as a diagnostic marker, the skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that would be useful as a diagnostic marker.

Moreover, just as in the *University of Rochester* case, discussed above, the present application discloses a broad genus of chemical compounds (polypeptides having 80% sequence identity to SEQ ID NO:14) but the claims are limited to only those compounds having a desired characteristic (wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells). Just as in *University of Rochester*, the present specification does not disclose which nucleic acids encoding the many possible polypeptides having 80% sequence identity to SEQ ID NO:14 are overexpressed in colon, lung, or prostate tumor cells.

Granted, those skilled in the art could screen libraries of naturally occurring DNAs for overexpression in colon, lung or prostate tumor cells to identify for themselves specific DNAs that encode polypeptides having 80% sequence identity to SEQ ID NO:14. That, however, does not make up for the deficiency of the specification's description. The *University of Rochester* court specifically noted that the patent at issue there disclosed screening assays to identify compounds having the desired characteristic, but nonetheless held that the description was inadequate. The same holds true here.

PRIOR ART

ISSUE

The Examiner contends that claims 72-74, 83, and 84 are anticipated by Young, and that claims 72-75, 83, and 84 are anticipated by Stanton.

Appellants contend that have demonstrated invention prior to the effective filing dates of Young and Stanton, and thus Young and Stanton are not anticipatory art within the meaning of 35 U.S.C. § 102(e).

Thus, the issue is whether the Declaration submitted under 37 C.F.R. § 1.131 is sufficient to overcome the rejections over the prior art made under 35 U.S.C. § 102(e)?

FACTS

The Examiner rejected claims 72-74, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Young (Answer 14).

According to the Examiner, Young teaches a polypeptide that shares 92.5% sequence identity with SEQ ID NO:14. (*Id.*)

The Examiner rejected claims 72-75, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Stanton. (*Id.* at 15.)

According to the Examiner, Stanton teaches a polypeptide that shares 96.7% sequence identity with SEQ ID NO: 14. (*Id.*)

Appellants do not argue the merits of the rejections. Rather, Appellants assert that the declaration submitted under 37 C.F.R. § 1.131 is sufficient to show invention prior to the effective filing dates of Young and Stanton (Br. 34).

Appellants cite the 37 C.F.R. § 1.131 Declaration of Dr. Goddard, Dr. Godawski, Dr. Gurney, Dr. Smith, and Dr. Wood, to support the proposition that the inventors "conceived and reduced to practice the PRO1866 polypeptide and its encoding nucleic acid sequence in the United States prior to December 4, 1998." (*Id.* (emphasis removed).) According to Appellants, "the Declaration clearly establishes that the claimed polypeptides and the nucleic acids encoding them, were conceived and reduced to practice prior to December 4, 1998, and that the differential expression of PRO1866 in the

multiple types of cancer cells based on microarray analysis were demonstrated prior to March 31, 2000." (*Id.* at 35.)

Appellants cite MPEP § 715.03 for the proposition that:

> proof of prior completion of a species different from the reference species will be sufficient to overcome a reference indirectly under 37 C.F.R. § 1.131 if the reference species would have been obvious in view of the species shown to have been made by applicants. Alternatively, *the applicant may be able to antedate the reference indirectly by demonstrating possession of the claimed genus prior to the reference date.* The test is whether the species completed by applicant prior to the reference date provided an adequate basis for inferring that the invention has generic applicability. . . . The test is whether the facts set out in the affidavit are such as would persuade one skilled in the art that the applicant possessed so much of the invention as is shown in the reference. *In re Schaub*, 537 F.2d 509, 190 U.S.P.Q. 324 (C.C.P.A. 1976).

(Br. at 35-36 (footnote omitted) (emphasis in original)).

Appellants cite their arguments regarding the written description rejection, asserting that the "disclosed polypeptide of SEQ ID NO[:]14 is *representative for a genus encompassing its variants*." (*Id.* at 36.)

Appellants also cite Example 14 of the Synopsis of Application of Written Description Guidelines issued by the USPTO, which Appellants note states

> that protein variants meet the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the

> specified functional activity and at least 95% sequence identity to the reference sequence.

(Br. 36.)

The Declaration submitted under 37 C.F.R. § 1.131 of Dr. Audrey Goddard, Dr. Paul J. Godowski, DR. Austin Gurney, Dr. Victoria Smith, and Dr. William I. Wood, dated October 26, 2004, states at ¶10 that "[b]oth the DNA-44174 and the PRO1866 polypeptide sequences were obtained prior to December 4, 1998." It further states at ¶17 that "the microarray analysis of mRNA expression of PRO1866 in cancer cells was conducted prior to March 31, 2000, and the data indicate that the mRNA of PRO1866 is overexpressed in colon, lung, and prostate tumors."

PRINCIPLES OF LAW

A declaration under 37 C.F.R. § 1.131 must establish possession of either the whole invention claimed or of something falling within the claim such as a species of a claimed genus, such that the claim as a whole reads on it. *See In re Tanczyn*, 347 F.2d 830, 831-32, 146 USPQ 298, 300 (CCPA 1965); *see also* MPEP § 715.02

Where the disclosure in the prior art is only a single species of a genus claim, appellant can overcome the rejection through the use of a 131 declaration by showing prior possession of the species disclosed in the reference. *In re Stempel*, 241 F.2d 755, 759, 113 USPQ 77, 81 (CCPA 1957). If the species disclosed in the reference is different from the species that was disclosed in the 131 declaration, the 131 declaration can only overcome the reference if the species shown in the reference would have been obvious in view of the species shown to have been made by appellant.

See In re Clarke, 356 F.2d 987, 961, 148 USPQ 665, 668-69 (CCPA 1966). If appellant cannot show possession of the species of the reference, appellant may be able to antedate the reference by showing prior completion of one or more species such that appellant was in possession of the claimed genus. *See id.* Note it is not necessary that the evidence demonstrate that appellant viewed the invention as encompassing more than the species actually made, only that the evidence would persuade one skilled in the art that appellant possessed so much of the invention as is shown in the reference. *In re Schaub*, 537 F.2d 509, 512 131, 190 USPQ 324, 326 (CCPA 1976). *See also* MPEP 715.03.

ANALYSIS

The species disclosed by the Declaration submitted under 131 is different than that disclosed by either the Young or Stanton reference. In addition, we have already determined in reviewing the rejection under 35 U.S.C. § 112, first paragraph, for written description, that the disclosure of a single species, *i.e.*, the polypeptide of SEQ ID NO:14 does not demonstrate that Appellants had possession of the claimed genus. Thus, we need to determine if the species disclosed by Young and Stanton would be obvious over the polypeptide of SEQ ID NO:14.

Appellants' claim 72 is drawn to a polypeptide having 80% sequence identity to SEQ ID NO:14. Thus, the species of Young and Stanton are clearly encompassed by the claims. Moreover, Appellants disclose that the polypeptide is overexpressed in colon, lung or prostate tumor cells. As we have already found above, however, neither the Declaration nor the disclosure as filed provides guidance as to what regions are necessary for

activity, or what the biological activity is, other than its use as a diagnostic marker. Thus, we conclude that there is nothing in the Declaration or the disclosure as filed that would suggest to one of ordinary skill in the art the species disclosed by Young and Stanton, and thus that the polypeptide of SEQ ID NO:14 does not render obvious the species disclosed by Young and Stanton. *See In re Baird,* 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.").

Thus, as the Declaration submitted under 37 C.F.R. § 1.131 is not sufficient to overcome the rejections over the prior art made under 35 U.S.C. § 102(e), the rejections of claims 72-74, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Young, and claims 72-75, 83, and 84 under 35 U.S.C. § 102(e) as being anticipated by Stanton, are affirmed.

CONCLUSION

In summary, we reverse the rejection of claims 72-79 and 82-84 under 35 U.S.C. § 101 as not being supported by either a specific and substantial utility or a well-established utility. We do, however, affirm the rejection of claims 72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification; the rejection claims 72-76, 83 and 84 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description; the rejection of claims 72-74, 83 and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Young; and the rejection of claims 72-75, 83 and 84 under 35 U.S.C. § 102(e) as being anticipated by Stanton.

AFFIRMED-IN-PART

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